CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

SCIENTIFIC CONFERENCE
"THE SCIENTIFIC CHALLENGE: FROM BASIC RESEARCH TO THE CLINIC"
THURSDAY, JULY 13, 2006
10:00 AM - 4:00 PM PDT
ROBERT M. MAHLEY AUDITORIUM, THE J. DAVID GLADSTONE INSTITUTES

On July 13, 2006, the California Institute for Regenerative Medicine (CIRM) held a scientific conference to discuss the scientific challenges associated with moving discoveries from the basic research stage forward to the clinic. This meeting was structured around a series of presentations (each followed by a brief question and answer period) by invited speakers, followed by a general discussion. This summary is not intended to be comprehensive with respect to reporting on this conference, but presents the discussion to the best of our understanding. This summary reflects the comments and opinions of the speakers; inclusion in this summary does not imply agreement, endorsement, or verification by CIRM.

Zach Hall, PhD; President, California Institute for Regenerative Medicine
Welcome and Introduction

- Dr. Hall Zach began the meeting with an introduction of the members of the California Institute for Regenerative Medicine (CIRM) staff, Independent Citizens Oversight Committee (ICOC), and Scientific and Medical Research Funding Working Group (SMRFWG) who were in attendance.

- He mentioned the four meetings involving the ICOC that will contribute to the development of the plan.
  - Slide 1 - ICOC Meetings
    - June 1/2, 2006: Mission Statement and Long-term Objectives
    - August 1/2, 2006: Values
  - Slide 2 - CIRM Scientific Meetings for ICOC Members and the Public
    - May 25, 2006: Funding Structures
    - July 13, 2006: Scientific Strategies

Stuart Orkin, M.D., Harvard Medical School
Chair, CIRM Scientific and Medical Research Funding Working Group
"Stem Cells: Looking Back and Ahead"

- Slide 1- Stem Cells: Looking Back and Ahead.
  - Dr. Orkin mentioned that he would suggest areas of focus for stem cell research.
  - Dr. Orkin co-chaired Task Force to evaluate NIH investment in gene therapy

- Slide 2 - Stem Cells: Laboratory to the Patient.
  - What do we need to know or think about?
    - The cells: Obtaining proper cells and learning how to utilize them in preclinical models.
    - The host: Learning how stem cells or their derivatives behave when introduced in tissues / organs.
    - The disorders we wish to treat: What are most promising conditions for treatment with stem cells or their derivatives?
    - Transitioning to the clinic: Synthesizing the above and navigating clinical regulatory environment, ethics, etc.

- Slide 3 - Some Historical Examples to Consider
  - Bone Marrow Transplantation (BMT): A cellular, stem cell therapy that is now 50 years old. How did it proceed in the "early days"?
  - Assisted Reproduction: A form of cellular manipulation that emerged on the public scene quickly.
  - Gene Therapy: Cellular and molecular therapy with a "checkered" history. What might we learn?

- Slide 4 - Bone Marrow Transplantation: The Early Days
  - A brief history of BMT by E.D. Thomas, the "father of BMT", from his Nobel lecture in 1991. Note that he started his work in 1955.

- Slide 5 - Bone Marrow Transplantation: Rapid Progress in the Early Days
  - Studies in dogs were published in 1971 showing improved survival using HLA matched donors especially in conjunction with the short term use of the immunosuppressive drug methtrextate.
  - By 1979, studies had been carried out with human leukemia patients that showed that a comparable treatment strategy also results in improved survival.

- Slide 6 - Bone Marrow Transplantation
  - BMT is a true stem cell success story founded on strong science and trial-and-error.
    - It was developed in animal models and the transition to clinical experiments occurred quite early on.

- Initial scientific advances largely out of the public eye.
- Initial failures were overcome by persistence. At least a 20 year timeframe was required before the procedures clearly successful; it is now mainstay of medicine.

- Slide 7 - An Interesting Date in Medicine: July 27, 1978
  - Prenatal genetic diagnosis by DNA analysis was first performed.
  - The first case of assisted reproduction was announced.
    - There was quite a controversy about the IVF case. A well known PhD in chemistry called the IVF birth a "stunt" and questioned whether or not experiments should even be allowed to continue.
    - Doctors also doubted the ethics of IVF; this is not much different than what we see now with stem cells.

- Slide 8 - *New England Journal of Medicine*, July 27, 1978
  - Abstract from the paper titled "Application of endonuclease mapping to the analysis and prenatal diagnosis of thalassemias caused by globin-gene deletion" by Orkin, *et al*.

- Slide 9 through 11- Headlines from *The New York Times*, July 27, 1978
  - "Scientists praise British birth as triumph."
  - "Doctors isolate a human gene allowing birth-defect detection."
  - "Religious leaders differ on implant."
  - "Successful laboratory conception intensifies debate over procedures."
  - "Infant in Britain reported to be 'normal'"
  - "Doctors doubt ethics in case of British baby."

- Slide 12 - Assisted Reproduction
  - Developed largely out of sight and outside the US.
  - The ethical outcry rapidly subsided as success of procedure became apparent.
  - Little regulatory oversight developed
  - Further advances occurred largely in the private sector.

- Slide 13 - *Business Week*, November 18, 1985
  - Featured an article titled: "The Gene Doctors - Scientists are on the verge of curing life's cruelest diseases."

- Slide 14 - Gene Therapy
  - Attempts to introduce expressible genes (DNA) into somatic cells in an effort to correct or modulate function(s) represents a challenge in "engineering" (that is, how to deliver genes efficiently and effectively to the desired cells) as well as biology.
  - Initially envisioned to be most useful for inherited disorders, such as sickle cell anemia, immune deficiencies (largely of the blood system). Soon thereafter, it was proposed for other inherited disorders, such as cystic fibrosis, and muscular dystrophy.

- The largest initial clinical efforts turned out to be in infectious disease (AIDS) and cancer

- Slide 15 - *The New York Times* Editorial, June 5, 1981
  - Headline "The Crime of Scientific Zeal"
  - After cloning of cDNA became possible, Martin Cline from UCLA performed a controversial gene therapy experiment. He was reprimanded and forced to resign after sending recombinant DNA to Israel which was subsequently put into the bone marrow of a patient.
  - It was becoming clear there were investigators who were willing to push the envelope, perhaps for laudable reasons but before general scientific and public acceptance.

- Slide 16 - *Chicago Tribune*, March 2, 1986
  - Headline: "Gene therapy reshaping our future."

- Slide 17 - Gene Therapy comic strip: NIH urges caution

- Slide 18 - NIH Review of Gene Therapy 1995
  - A panel of scientific advisors informed the NIH that gene therapy has been "oversold" by researchers and journalists citing nearly uniform failure of the procedure.
  - What was needed was a return to the lab to do basic work prior to trying out "long-shot" therapies in patients. There was a need to go back almost to square one.
  - Dr. Harold Varmus (the Director of the NIH at the time) made an effort to "calm things down."

- Slide 19 - *The New England Journal of Medicine*, April 18, 2002
  - Paper titled "Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy" by Alain Fisher, among others.
  - The researchers used gene transfer to cure X-SCID. This involved no new science, but rather applied existing science. It looked like a success for gene therapy.

- Slide 20 - *Science*, March 2005
  - A panel urged limits on X-SCID trials, due in part, to the development of T-cell leukemia in 3 of 12 children treated.
  - The delivery vector that researchers were using to introduce the gene to treat X-SCID inserted into the chromosome, in some instances, in a site where regulatory elements in the vector drove the uncontrolled expression of a proximal chromosomal gene involved in cell growth. This cooperation was powerful enough to create a leukemia phenotype.

- Slide 21 - Reports and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy
  - Could the results of the X-SCID gene therapy trial have been predicted? As noted in the excerpt from the 1995 report on gene therapy to the NIH shown on this slide, this possibility was foreseen. Preclinical studies in animal models could potentially been

predictive, but there was not enough of a focus on the long-term effects of gene therapy in animal models.

- Ultimately, as the report stated, in part: "Because clinical experience is still so limited, it is not possible to exclude long-term adverse effects of gene transfer therapy….Only longitudinal clinical follow-up of treated patients can provide data on the long term safety…."

- Slide 22 - Gene Therapy: Where Are We Now?
  - We know it "works" in the proper clinical settings with attention to details, but, as with all therapies, there are serious, potential complications, some of which could have been anticipated.
  - There have been some promising findings in other types of X-SCID, in host defense disorder (chronic granulomatus disease), and in forms of hemophilia.
  - Prediction: gene therapy will ultimately find a place in medicine, but applications for the near future are likely to be limited to rare disorders, rather than more common diseases.
  - The prospect for this therapy may change radically if methods are developed to repair / correct genes *in situ* rather than merely adding genes randomly, as has been done to date.
  - With respect to timeframe, to date, we have seen over 25 years of effort with checkered success.

- Slide 23 - Comparisons of the Stem Cell Field to Others
  - As with BMT and assisted reproduction, stem cell therapy offers the potential for a large, positive impact on human health exists
  - More so than BMT or assisted reproduction however, stem cell research is conducted under the "microscope" of public scrutiny.
    - Regulatory oversight and guidelines were introduced early in the evolution of the [stem cell] field; BMT, until recently, was largely regulated by its practitioners while assisted reproduction is largely un-regulated.
    - Intellectual property considerations were also introduced earlier; there is some debate about whether this will inhibit applications.

- Slide 24 - Highest Priority Areas for the Stem Cell Field
  - Identifying and characterizing stem cells in different organ systems and then asking:
    - Are there stem cells?
    - How do we isolate them and study their properties and capabilities?
    - What is the niche of stem cells in different organs?
  - Delineating the pathobiology of target diseases and then asking:
    - What is the role of stem cells?
    - What do stem cells (and / or their descendents) offer?
  - Elucidating self-renewal in stem cells and ultimately harnessing cellular reprogramming and directed differentiation

- Developing real-time, informative methods for examining fate, behavior and function of stem cells following introduction into animal models or patients; experiments must inform the science, not just provide a "yes or no" answer.

- Slide 25 and 26 - Challenges Going Forward
  - Developing the infrastructure for proper characterization, maintenance, and expansion (or differentiation) of stem cells for clinical use (not only in the lab but also the regulatory and intellectual property infrastructure). These efforts might include:
    - Creation of embryonic stem cell banks
    - Creation of training centers
    - Exploration of alternative means of embryonic stem cell generation
    - Development of antibodies for isolation of subsets of cells and adult stem cells
    - Development of GMP lab(s) for cell expansion.
  - Designing preclinical studies that provide maximum, relevant data for the transition to the clinic. These efforts may focus on:
    - Developing appropriate animal models of diseases.
      - The key is to choose the animal model that is most useful for what you are studying; mice models are at times most suitable and primate and dogs models are also good.
      - Any animal that can mimic the disease in question but do it in an accurate fashion may be suitable.
    - Imaging of introduced cells *in vivo.*
    - Creating an "animal hospital".
    - Studying toxicology.
  - Designing clinical studies that provide real-time surrogate measures of in vivo effects. This may involve:
    - Fastidious design with real-time surrogate measures
    - Development of "translational labs" for assays of relevant biomarkers
    - Careful but balanced oversight
    - Involvement an of pharma expertise and support
  - Balancing the prospects for success and the realities of potentially inadequate therapy or serious "side-effects" in treating life-threatening or debilitating disorders.

Jill Heemskerk, Ph.D., National Institute of Neurological Disorders and Stroke
"The SMA Project: A New Approach to Therapy Development at NIH"

Presentation

- Slide 1 - Title Slide
  - This new NIH program is designed to stimulate the translation of basic science findings into the clinic and although it happens to be a drug discovery development program, many of the lessons apply broadly to any kind of translation effort.

- Slide 2 and 3- Industry Neurotherapeutics: 19 Disorders
  - What motivated us to branch out in this area, which is not normally a heavy NIH focus?
    - A survey conducted by PhRMA (Pharmaceutical Research and Manufacturers of America) in 2003 showed that while there were almost 200 medicines for neurological disorders under development at that time, the number of neurological disorders targeted by these medicines was only 19.
    - At the same time, there are over 450 NINDS disorders. The diseases focused on by industry versus the total number of neurological diseases leaves a large gap.

- Slide 4 - The SMA Project
  - What is it?
    - A $22M, 4-year NINDS therapeutics program for Spinal Muscular Atrophy (SMA), a paralyzing disease of childhood caused by the deletion of specific gene that affects motor neurons.
    - The program is also considered a pilot for other rare diseases.
  - What is its goal?
    - To advance new drugs for testing in SMA patients

- Slide 5 - Rationale for SMA as a Pilot
  - There was a "constellation" of reasons why SMA seemed tractable for therapy development and a perfect disease / niche for NIH to step into and:
    - There was a defined cause: the loss of SMN1 gene
    - There was a defined strategy for treatment: increase expression of SMN2, an identical protein that is normally expressed at lower levels.
    - The was a defined focus: the study of compounds that increase SMN2 expression
    - Much good work had come from gene expression models in mice and provided a proof of principle.

    The patient population was not large enough for industry to step in.

- Slide 6 - SMA Project Focus
  - Our focus is on things that are normally confined to industry.
  - We are not doing clinical testing; anything we generate will be moved to clinical testing outside of the program. We hope for increased industry interest if the program successfully advances drugs to the point of readiness for testing in patients

- Slide 7 - Scientific Steering Committee (SSC)
  - The SSC's composition is very unique. It includes very senior medicinal chemists and biologists who cumulatively have over 100 years of high-level industry experience.
  - There are also translational and clinical experts on the SSC as well as representation from the FDA.
  - We actually avoided having expertise from the field we're targeting; these are not SMA researchers but academic neurobiologists whose expertise is relevant.

- Slide 8 - NINDS / SAIC Structural Model
  - Basically, the SMA project is a virtual small pharma company in practice; as a group, it supplies all the activities that need to go on in a small pharma company, like chemical optimization, testing, pharmacology and toxicology, etc.
  - We also have the ability to do late stage IND enabling studies.
  - We have contracts in place to bridge where academia leaves off and clinical studies begin.
    - There are contracts to four sites along with primary contract to a company called SAIC for project management.
  - The glue in the program, in addition to project management, is a web accessible database set up through CambridgeSoft (under contract) so NIH, contractors and consultants can access data provided by the sites from the archive in real time.

- Slide 9 - Lead Development Team
  - The lead development team is a group of hired consultants that helps us on a weekly and monthly basis to evaluate data coming from contract sites, interpret it and revise strategy so the work is integrated and coordinated and flowing along.
  - They take the activities of a group of individual contactors and act as a hub to coordinate information.

- Slide 10 - SMA Project Drug Discovery & Development Testing Funnel
  - We have a testing funnel for work flow.
    - It is a funnel since chemists produce hundreds of compounds and perhaps one comes out of the funnel.
    - There are incremental rounds of synthesis and testing until the compound is ready for *in vivo* testing in animal.
  - Compounds that make it thorough and look very drug-like and have good activity will go through preclinical IND enabling studies

- In any situation with an iterative process where repeated optimizing and testing occurs, this is where the time component really lies.
  - What we have is a one week cycle where data gets submitted to the database.
  - We have done 36 of these cycles for the first scaffold.
- Watching the lead development team has been an important learning experience on how to accelerate the whole process.

➢ Slide 11 - Starting Scaffolds
- We are in our third year and are starting to optimize two scaffolds.
  - Indoprofen
    - Increases SMN protein in vitro (Lunn et al, 2004)
    - Improves *in utero* survival of SMA mice (Lunn et al 2004)
  - Phenylbutyrate
    - Increases SMN expression in vitro (Andreassi et al 2004)
    - Extends survival of SMA mice (Burghes, unpublished)

➢ Slide 12 - Indoprofen Structure Activity Strategy
- The chemical optimization process is called SAR (Structure Activity Relationship) studies. The goals are:
  - To increase the potency of the molecule.
  - Eliminate toxicity (due to COX inhibition activity of the drug).
  - Improve blood brain barrier (BBB) penetration and ability to reside stably in the brain.
- Chemists look at molecules and see where they can make changes that could impact properties including activity. Chemical optimization is an informed iterative process with the outcome of any change not entirely predictable.

➢ Slide 13 - Indoprofen SAR is Tractable
- We have produced and tested 552 analogs in a bioactivity assay.
- 145 of these analogs show improved activity in the assay.

➢ Slide 14 - Improved Brain Distribution
- SMA is developing indoprofen analogs with greater brain to plasma ratios to facilitate delivery into the brain.

➢ Slide 15 - Improvements to Indoprofen
- A number of successes have occurred:
  - Increased potency 200 fold
  - Increased efficacy 2.5 fold
  - Enabled brain delivery
  - Abolished the part of the structure responsible for COX inhibitory activity.

- A provisional patent application has been filed for indoprofen analogs for treatment of SMA.
- The compound has moved into *in vivo* testing and SMA hopes to get results from mouse studies soon.

- Slide 16 - Systematic In Vivo Testing
  - Pharmacologic Studies
    - Formulation
    - Oral bioavailability
    - Brain distribution
    - Maximum tolerated dose
  - SMA Mouse Model
    - Survival
    - Body weight
    - SMN expression studies

- Slide 17 - Getting to Patients
  - SMA Project Studies
    - Characterize and improve drug-like properties.
    - Perform rigorous safety studies.
    - File the IND for clinical testing when we get a clinical candidate.
  - The end goal is getting a drug for patients.
  - Looking beyond the SMA project:
    - We may or may not perform early phase clinical trials to attract industry.
    - We are beginning to advertise to industry that we have a licensing opportunity and hope they will pick it up for full development.

- Slide 18 - "Industry-style" *not* Industry
  - This is not industry; it is an industry-style program.
  - The SMA project is a collaborative enabler with the goals of enabling therapeutic discovery, not being competitive with industry.
  - We can enable industry drug development by:
    - Developing licensing opportunities (e.g., indoprofen analogs)
    - Enabling outside efforts that are IP -neutral.

- Slide 19 - Lessons Learned
  - The steering committee provides structure to the program and its selection was critical.
    - Industry advisors.
    - Fresh scientific perspective by going outside the SMA field.
  - Industry style operation

- Flow plan with a clear set of experiments and advancement criteria is very important to keep the project on track and monitor progress.
- Service organizations provide rapid turnaround.

▪ Intensive project management
- Tight, centralized coordination of projects.
- Internal expertise (Lead Development Team).

▪ Balance academia where speed and throughput is not the primary goal.

➢ Slide 20 - Applying the Pilot to other Diseases
▪ NINDS is so happy with the pilot program it is broadening it to other neurological areas.
▪ A neurotherapeutics program is coming in 2007 and will feature many of the things missing from many primarily academic neurological translational efforts:
- Medicinal chemistry service facility
- Central NIH project management
- Flow plan-driven projects
- Resource leveraging

▪ We can't spend $22M on each disease so to make this cost effective and nimble we will engage biologists in the field to provide the disease specific biology
▪ The NIH now has programs that fund late state pre-IND enabling studies like pharmacology and toxicology, so a lot of that can be done outside our program now.

Discussion

➢ **Q (Burt Lubin; Children's Hospital, Oakland)**: How did you choose this disease?
▪ **A:** There were strong lobbying efforts, but the choice was driven by "scientific readiness". Neurological disorders are genetically very complex. It is hard to get evidence on therapeutic mechanisms. Here was one disease that was genetically very simply with a lot of proof of principle from animal models and cell studies, so everything was in place. Now there are a few other diseases that probably meet the criteria that will be necessary.

➢ **Q (Don Reed):** What is the COX inhibitory structure altered? Do you have any advice for orphan disease advocates as to how they can work together to increase their clout.
▪ **A:** That part of the molecule that confers COX inhibitory activity is described. We've changed it structurally and have considered that inhibitory activity to be gone, but we need to test it. There is power in patient advocate organizations stimulating this effort. The ALS associate is a great example. It is a small disease but with a good coordinated effort. They have an internal program with features of the SMA project. Other foundations have projects similar to SMA.

- **Q (Patricia Olson; CIRM):** Are these resources available to all investigators?
  - **A:** The biological testing is on a very tight schedule. There are not many biological assays amenable to that kind of turnaround and not many labs that can spare the resources to do this. This kind of structure will limit the number of diseases that can make use of the program. Other diseases can look at our program as a model and make use of our program over time.

Allen M. Spiegel, M.D., Albert Einstein College of Medicine
"Delivering on the Promise of Stem Cell Research: What will it take?"

Presentation

- Slide 1 - Delivering on the Promise of Stem Cell Research: What Will it Take?
  - I believe in the enormous promise of embryonic stem cell research, but I can't tell you definitively what it will take.

- Slide 2 - Fifty-seven year old woman diagnosed with Type 1 Diabetes Mellitus (T1DM) in 1950 (brittle)
  - I will focus my talk on Type 1 diabetes (or what used to be called juvenile diabetes), because many of the issues we'll have to deal with in stem cell research play out in the arena diabetes.
    - My entrée into the stem cell question took place at a Senate Appropriations committee when I was facing questions from Tom Harkin about the Edmonton Protocol for the use of islet transplantation as a cure for diabetes.
      - An example of the protocol is a procedure performed on a 57 year old woman using islets from cadavers, which raises the issues of immuno-rejection.
      - Her case typifies the tight rope for people with Type 1 diabetes: high sugar levels leading to coma and low blood sugar potentially leading to death.
      - We currently spend $18,000 per year on immunosuppresants; there is a downside to being on these immuno suppressive drugs.
    - There are problems with the current presidential lines as they have all been exposed to mouse feeder layers.

- Slide 3 - The Science and Public Policy of Stem Cells
  - Biology, ethics / religion, and politics all influence stem cell research.
  - Too often politics clouds the discussion of biology and the science.

- Slide 4 - The Promise of Stem Cell Research
  - This is the primer that was brought into the Oval Office in August 2001.
  - We need to be humble about the unknowns and learn the lessons from gene therapy about overpromising from a timeframe standpoint and about what can be delivered; this needs to be about hope, not hype.
  - There are many different potential application of stem cells:
    - Identify drug targets and test potential therapeutics
    - Toxicity testing
    - Tissue / cells for transplantation
    - Study cell differentiation which may lead to an understanding prevention and treatment of birth defects.

- Slide 5 - Stem Cell and Developmental Biology Writing Groups
  - At NIDDK, we created Stem Cell and Developmental Biology Writing groups that included NIDDK advisory council members to assist in focusing efforts with respect to our stem cell strategic plan.
  - They illuminated some of the key challenges for us.

- Slide 6 - Challenges
  - Developing new methods for recovering stem cells as well other cell populations necessary to maintain "stemness" ex vivo.
  - Developing new ways of assaying stem cell functions both *ex vivo* and *in vivo*.
    - This underscores the importance of imaging studies to track stem cells in vivo.
  - Integrating genomics, proteomics, and bioinformatics to characterize molecular features of stem cells and their committed daughters.
    - That challenge led to a specific recommendation to create stem cell Genome Anatomy Projects (GAPs).
  - Developing new *in vivo* models for studying stem cell function
    - We often have mouse models for disease, but they are often flawed due to timeframe with which they evolve or manifest pathological characteristics. We need to develop models that better reflect human disease.

- Slide 7 - Proactive Role of NIDDK
  - The recommended role for NIDDK was to be proactive in:
    - Development of enabling technologies and knowledge base.
    - Launching research initiatives that connect stakeholders from multiple disciplines across the country as the scope / scale of science is rapidly expanding in the early post-genomic era.
    - Provide a means for making biological reagents from model organisms and humans available to the research community.
    - Assure adequate training of scientists and physician-scientists in areas supportive of stem cell research.

- Adequate education of the public concerning the importance of this area of investigation.

- Slide 8 - Recommendation
  - "NIDDK should catalyze a nation-wide effort to characterize the molecular and cellular features of stem cells during and following development of the pancreas, liver, stomach and intestine, kidney and GU tract, bone and hematopoietic tissues."

- Slide 9 - Using Diabetes and the Pancreas as a Paradigm
  - Pancreatic islets contain insulin secreting beta cells, but there is difficulty in harvesting these cells in a viable form and injecting them into the portal vein to seed the recipient liver.
    - We can't do this justifiably in kids with current technology because the immunosuppression is too drastic, so a long-term goal is achieving immune tolerance.
    - Also, if you do the math, the supply of cadavers would never be adequate, so we needed an unlimited supply of these cells.
    - One of the attractive features of this disease is, in principle, getting hormone in blood stream is all this gland [the pancreas] needs to do. The notion is all you need is access to the blood stream for the sensing device for the parameter being regulated (like blood glucose) and for the hormone to be delivered.
      - It's never as simple as that, because the Beta cell, which delivers insulin and senses glucose levels, lives inside a complex structure called the islet. If we could just get the Beta cells from stem cells, would that be sufficient or do we need to replicate the islet? Also, is the liver the best place for delivery? There are many complex issues.
      - Think about this in comparison to Parkinson's or neurological disorders where the right neural connections need to be made; I would argue that's substantially more complicated.

- Slide 10 - Obstacles and Opportunities in the Road to an Artificial Pancreas: Closing the Loop.
  - The idea of in-dwelling glucose sensing insulin pumps will happen, but this will never be as good as what evolution and nature have done i.e. an islet.

- Slide 11 - Pancreatic Islet
  - The pancreatic islet includes insulin secreting Beta cells and glucagon secreting Alpha cells. There is also an interesting and important architecture.
  - The minimum for therapy is to get these insulin secreting Beta cells, but the ideal is to reconstruct the islet.

- Slide 12 - Beta Cell Biology Consortium (BCBC)
  - One of the major initiatives that emerged form this strategic planning process was the Beta Cell Biology Consortium.
  - My feeling there is there is much to recommend this type of funding structure and initiative for some of the things you may want to do in CIRM.
  - Features of this BCBC (which is in its second iteration after peer review, has external advisors, and has benchmarks and milestones but is different from an industry model).
    - Mission: To facilitate interdisciplinary approaches that will advance our understanding of pancreatic islet development and function.
    - Goal: To develop a cell-based therapy for insulin delivery.
    - It has both intramural and extramural components.
    - It has focused initially on the basics of developmental biology and creating the tools to advance this field.
    - Some doubted that this would work because institutional barriers wouldn't allow collaboration [across institutions] to happen.
      - We need to look beyond parochial issues and look at the broader picture.
      - Someone once said, if you want to herd cats you need fish (read money); if you put enough money out there you will get some of these people to collaborate.
    - These are interesting issues for CIRM to face, but how this will align and what the regulatory issues will be remain to be seen and will color these issues
    - Competition is good. You want a structure where there is a lot of opportunity for competition, creativity, and innovation, but at the same time, especially for enabling tools, you need a level of collaboration that hasn't routinely existed.

- Slide 13 - Beta Cell Biology Consortium Website
  - There are two levels on the website: one that only investigators can access and use to access and share data and data mine and one that is open to the public.
  - Some of the funding we did was for pilot and feasibility studies not reviewed by ourselves (NIH) but by people running the BCBC so they could bring in outside people and fresh ideas to allow innovation to occur.
  - We did not lose sight of the fact that antibodies to cell surface proteins are essential components to ESC research and a major core within this facility focusing on antibody development. We also need to identify cell surface proteins to move this field along.

- Slide 14 - Current Research of Beta Cell Biology Consortium
  - Determine the temporal expression and function of genes during pancreatic islet development.
  - Develop tools to identify and prospectively isolate pancreatic stem / progenitor cells.
  - Identify factors that can drive stem cell differentiation toward pancreatic progenitor lineage.

- Slide 15 - Pancreatic Islet Production
  - Overview of pancreatic islet production

- Slide 16 - Converting ESC into Beta Cells
  - We still have much to learn about the factors that can drive stem cell differentiation.
  - Specific transcription factors that characterize various stages of differentiation have been identified and these could theoretically be transfected as candidate genes into precursor cells or as external signals.
  - One school of thought is we should apply a high throughput industry-like approach to this stage for things like growth factors, media, and reagents; another says we should drop back and do it the slow motion biology way where we will learn more but it will take a lot longer. This is a tough question and I don't know the answer.

- Slide 17 - Beta Cell Development
  - M. Gershengorn is now conducting research on islet and Beta cell development. He has a paper in Science where he isolated precursor cells from human islets that *in vitro* de-differentiated and then could be brought back to an insulin secreting glucose sensing phenotype.
  - This suggests it is possible to short circuit the long road to ESC differentiation.
  - We need to understand the various pathways using vigorous methodologies. There's an important virtue in understand this route in depth in hESC.

- Slide 18 - Can pancreatic islet function recover in patients with long standing T1DM?
  - Data suggesting this is possible:
    - Functional: Persistent insulin production years after T1DM onset
    - Anatomical: Autopsy series showing pancreatic beta cells years after T1DM onset
    - Immunological: Immune cells "armed" for beta cells found in the lymph nodes that "drain" the pancreas years after T1DM onset
    - Can you then stimulate and allow endogenous regeneration? This requires:
      - Safer, more specific immune interventions.
      - Understanding how we can stimulate this more effectively and the steps that allow an ESC to become an islet.
  - There are technological advances allowing us to test this hypothesis:
    - Functional: It is now possible to "tightly" control blood sugar.
    - New, safer, and more specific immune interventions.
  - Other Technical advances under development:
    - Anatomical: Techniques for measuring beta cell number in humans.
    - "Supply Side": Agents purported to stimulate new beta cell growth in rodents.

- Slide 19 - Intervention trial testing islet recovery hypothesis
  - Clearly we need a lot more pre-clinical work before going into patient scale protocols.
  - This work will well help determine the path for getting to Beta cells.

- Slide 20 - The Scientific Challenge of Human Stem Cells: The Basic Research Phase

- Slide 21 - The Cell Therapy Bench to Bedside Process

- Slide 22 - Cell Science versus Rocket Science
  - Curing a disease like Type 1 diabetes, doing embryonic stem cell research, or doing cell therapy is not rocket science; it's a lot harder.
  - There are engineering aspects to cell biology that we have get right such as scale up and delivery.
  - People who are passionate about curing these diseases tomorrow need to understand we will only set the field back if we plunge in and do it in a premature way. We need to move ahead with all speed but with diligence, with rigor, and with safety in mind.

Discussion

- **Q (Bob Klein; Chair, ICOC):** Looking to California, in the area of diabetes, is there a special contribution we could make because of the biotech industry or non-profits, with the funding stream that is in place, where we can provide a more critical input that may be more difficult for other institutions in the country?
  - **A:** Absolutely.
    - There is a valley between where industry is interested and where academic and NIH support has traditional gone. This relates to many aspects of Type 1 diabetes in particular; industry is reluctant to get involved in this area, but Type 2 diabetes is seen as more of a blockbuster. But there are a number of reasons why industry is unwilling to enter this field:
      - Experimenting on kids is not appealing to industry
      - The business model is not appealing. Think vaccines - a one time treatment for diabetes eliminates the need for insulin injections and this is not of interest to big pharma. There are small companies that would be willing to pursue this, and the principle role for CIRM here would be to fill in and decrease risk for industry to get involved by investing in pedestrian preclinical toxicity studies that the NIH has typically has trouble supporting.
    - The NIH is trying to move forward in this area with the RAID (Rapid Access to Intervention Development) program. It is not a grant program but a contract based mechanisms in which you could get access to contract resources for toxicity, for example. This is a real bottleneck.
    - The large scale production of recombinant proteins is another bottleneck. This is true as well at the industry level. The NCI was not able to address this.
    - The bottom line is we need to identify areas where NIH and academia are not as active because the work is not as hypothesis driven and perhaps too costly and where industry is not willing to come in because of the risk involved. In theory you could toss money at this. But you need to look at it with rigorous criteria to see if a partner be willing to pick it up. Filling in middle ground would be important.

- **Q (Ed Penhoet; Vice-Chair, ICOC):** Are there rules for membership to BCBC? Who decides who is part of the Consortium? What are the sharing rules for things like information and intellectual property?
  - **A:** The BCBC website is a way to share in depth information. We have been through two iterations of the Consortium, with the first involving a peer reviewed mechanism where people brought projects to table they thought were relevant. In the second iteration, some members dropped out or were felt not to have met milestones, some members were retained, and new ones were brought in. There are definitive rules for sharing data at various levels. This gets into other issues in terms of IP and we're not oblivious to this. We also need to ask what this means for the career of a grad student who needs a first authored paper where the data isn't given out first. There are issues about the academic culture and the reward system we have to deal with.

Stephen A. Sherwin, M.D., Chairman of the Board and CEO Cell Genesys, Inc.
"The Development of Novel Cellular Therapeutics: Some Lessons from the Private Sector"

Presentation

- Slide 1 - The Development of Novel Cellular Therapeutics
  - In many ways what I have to tell you is not specific to stem cells but relates to other products based on novel technologies. The common question is: what's involved in taking a concept in basic biology forward and putting in the hands of doctors so they can benefit patients?

  - I can share three lessons:
    - It takes a long time and a lot of money to take an idea from the lab and advance it through development and put it in the hands of doctors and patients. It will take longer and cost more than anything you can possibly imagine, so you need to plan for that.
    - You also have to be willing to change direction quickly, and not just based on data, but because your approach can rapidly become obsolete. It's a hard concept to grasp in this area because stem cells are cutting edge, but there are a lot of talented people working on the same disease targets using different approaches. You have to be cognizant of this and be willing to change direction quickly.
    - Collaboration is essential in areas so focused on development, particularly ones that are new technology driven and focus on complex biology. This can be done through an alliance or a merger. You have to be willing not to have the NIH syndrome. (Nothing Invented Here).

- Slide 2 - Cell Genesys Today
  - Cell Genesys has been around for 17 years.
    - We began with a different picture of the opportunities - we were a technology development company and we weren't interested in products. We were trying to harness new genetic technologies.
    - Today we are very a product focused company; our lead product is a cellular immunotherapy for prostate cancer made of living, modified cells. This product is in international Phase III trials. If this is successful it will have cost not tens but hundred of millions of dollars to develop and that's not above average.
    - We had to be convinced this was worthwhile and we were convinced. You will have to make decisions based on the nebulous notion of conviction, which may or may not be an analytical process.
    - These products can't go anywhere if they can't be produced at scale with reproducible methods that allow you to characterize the products adequately in a manner that fulfills the regulatory requirements.
      - We made a huge bet and today have a facility producing these products at scale in California, which required an investment in excess of $50 million.
      - By having that in place, we were able to go to the FDA and say "this is how we will make the product if we're successful in trials" and we negotiated those details *before* we treated the first patient in the Phase III trial.
      - So we don't have the issue of going back to them after the trials and saying this is how we'll do it
    - A complex biologic can and will change based on the process by which and location where it is made. CIRM needs to pay attention to this aspect of product development. We made an investment in infrastructure *before* we had the data that would convince anyone to make that investment; CIRM will have to make the same decisions.
    - One thing we did successfully is we have spun out two companies and sold off assets not central to our business such as Abgenix (which develops antibody technology), which we spun off in the mid 90s and was recently acquired by Amgen for $2.5B.
      - There are probably going to be assets that aren't central to the Institute's principle research strategy where it's wise to think about how to harvest value and bring money back in. That might be a good tactic.
      - We have another spin off that is still a private company called Ceregene which is exploiting some of our technologies for use in Parkinson's and Alzheimers.

- Slide 3 - The History of Cell Genesys
  - In the early years we were involved in technology development and working on new technologies for therapeutic proteins and monoclonal antibodies, but we always had a principle focus in cellular therapy.
    - We started to develop T-cells for HIV treatment. Despite early clinical successes, this therapeutic approach became obsolete in the mid-90s when treatment went from the use of reverse transcriptase inhibitors alone to the use of transcriptase inhibitors and protease inhibitors. The attention of the patient and clinical community shifted so we stopped this program and restructured:

- We spun out our antibody area to raise capital and acquired Somatix. This shifted our focus from HIV to cancer and the only way to do that quickly was through a dramatic shift. It also shifted us from patient specific therapies to off-the-shelf therapies.
- Then we turned our attention to the focus we have today, the investment in manufacturing and clinical development.

- Slide 4 - So What Do Biotech and Home Remodeling Have in Common?
  - Like home remodelling, efforts in biotech take twice as long and costs twice as much as you expect.

- Slide 5 - A Specific Example: Amgen's Panitumumab
  - The biological rationale for Amgen's monoclonal antibody panitumumab as a potential cancer therapeutic was well known when product development began. It's not the first antibody targeting the EGF receptor, so the biology was reasonably well understood, but this still took eleven years from selection of the product candidate to get to FDA submission.

- Slide 6 - Another Specific Example: Genentech's Avastin®
  - When the biology is not so well known, as with Genentech's monoclonal antibody Avastin®, it's much harder; Avastin® took 30 years to develop; it's either 30 years if you include the time required to understand the biology or 17 if you don't.

- Slides 7 through 10 - The Twenty Year Lesson!
  - You can measure success by the number of approved products, the number of therapies, the number of patient being helped.
  - If you look at other products, this graph shows this process is not peculiar to antibody products, but shows how long it has taken to achieve success for the development of protein and antibody products as well.
  - Gene and cell therapies will likely parallel the development of protein and antibody products and real success will likely come mid to late next decade.
  - The reason I think we can start to say we're coming off the baseline in cell therapies is because of the data we're getting out of some clinical research. A line for stem cell therapies alone, rather than gene and stem cell therapies combined, would be shifted to the right, indicating a longer timeframe for success.
  - This is what I mean by "managing expectations" - making sure everyone understand the timeline associated with the development of complex biological therapeutic products.

- Slide 11 - Why Does It Take So Long?
  - I don't have anything profound to say here, but:
    - All new technologies face challenges, but they come on the scene full of hope and expectations with no reality testing about what they can't do. Then we have this sort

crash when reality steps in. It's particularly hard on patients and patients' families, so managing expectations around this is critical.

- Slide 12 - Technology Challenges
  - We learned pretty quickly that it's one thing to make insulin in *E coli* and quite other to make more complex proteins in mammalian expression systems.
  - For gene therapy, the issue has been safe and efficient delivery systems. I think we have progress now
  - Manufacturing and product characterization at pharmaceutical scale is also rate limiting.

- Slide 13 - Clinical Challenges
  - This is always hard and getting harder. The regulation and oversight of clinical research is more complex every year and more agencies have stake in it.
  - It's even harder in chronic diseases because the measure of efficacy takes longer and is often less precise.
  - The other side of the coin is long-term safety; these two things converge to create the size, duration, and cost issues of Phase III development.

- Slide 14 - Regulatory Challenges
  - If the organizational structure of FDA doesn't change, cellular therapies will be overseen by Center for Biologics Evaluation & Research (CBER) and the Office of Cellular, Tissue and Gene Therapies (OCTGT).
    - You couldn't find better motivated people, but I can speak to CBER that they are woefully under resourced and understaffed. They can barely keep their heads above water in terms of the day to day work of reviewing applications without dealing with the crisis of the day that gets layered on top of that.
    - The solution is not adding to the user fees, it's a dramatic intervention of the sort that benefited the NIH, specifically, increasing Congressional appropriations for the FDA.
    - I'm on the Board of the Biotechnology Industry Organization and today we announced an initiative to support increased appropriations for the FDA and I would urge this Institute, as appropriate, to do the same.
    - If we can do that, we can then get this part of the FDA to develop the guidance documents for guiding the manufacturing and quality control testing of these products. It takes along time for the agency to develop new regulatory policies and I'm sure they will need it for the stem cell area. There are forthcoming guidance documents for what are called adaptive clinical trials and those could be very helpful.

- Slide 15 - What Are The Potential Solutions?
  - To reiterate:
    - Plan for longer timelines and more expensive programs (and manage expectations)
    - Be willing to turn on a dime
    - Dismantle all signs of ego and collaborate

- Slide 16 - What Can The Private Sector Do?
  - Any successful collaboration starts and stops with understanding what you bring to the table and what you don't.
    - The private sector is pretty good at the practical aspects of large scale product development and commercialization. I don't think we play to our strengths by trying to do basic discovery research. This Institute can do that, and I wouldn't advise CIRM to self-fund a large scale manufacturing facility by itself.

Discussion

Q (Claire Pomeroy, Dean, UC Davis School of Medicine): There has been a lot of discussion about CIRM's IP policies, which must include a return to the state of a portion of the moneys, and some of the feedback we've gotten from private industry is that this will discourage collaboration. Can you give us your feelings about those guidelines and how we can incentivize academic and industry partnerships?

A: Two points:

- First, at end of the day, it's all about numbers - what is the royalty burden that will be imposed on the private organization? What do they have to pay back?
- Second, for the most part, mature organizations with a track record in development and commercialization would much prefer an up-front, one-time payment that is considered to be a fair net present value considering the risks associated with the value of the commercial rights. That way, there isn't the trailing impact of royalties throughout the life of the products which are difficult to comprehend and manage form a business standpoint.
  - I would urge, with appropriate 3rd party advice, that you consider not just routine royalties but the buy-out of royalties as a concept
  - In the end, it's all about the numbers. There are some in the private sector that say "if you charge us anything it won't work" and I don't believe that. Every company has royalty obligations. It's all about the numbers

Q (Bob Klien): What are adaptive clinical trials?

A: It's hard for me to give a lot of details as all that's been put forth is the concept and the regulatory guidance documents are forthcoming. The individual working with this at FDA is Scott Gottlieb; you should touch base with him.

- The notion is to use pharmacogenomic information as you go along. If you find a subgroup of responders, this approach allows you to change your design even in the middle of a registration trail (which would be a new concept) and adjust the sample size accordingly based on identifying this subpopulation that may respond better and excluding the subgroup that has an unexpected, undesirable toxicity. That's the main theme of what I've read but it's still early days.

Q (Rich Voliet, UC Davis School of Veternary Medicine): If you take monoclonal antibodies, and everyone in this room would agree they are a "silver bullet", they showed a 25 year period before they were effectively used in the clinic. What can we learn from that experience? It's

inexcusable that it took 25 years to get a very effective treatment into patients. What can we learn from that experience to avoid it in stem cell therapy?

A: It's the question of the hour and what I tried to make the theme of my presentation. I think we can look back at the history of therapeutic product development based on new technologies and the pattern in remarkably repetitious. You cited antibodies but you could say the same thing about proteins and gene therapy and cell therapy.

- With respect to antibodies, the things I think are important are there was an inadequate acceptance of the limitations of the technology in the early days and a conviction that it really doesn't matter that these are mouse proteins because we will find clinical settings in which it isn't going to be problem for the patient.
- What I would have done differently is to have, in parallel with early clinical testing, assumed the technology development needed to go on because it was inadequate. The problem is, if you've invented a technology you're sure you've arrived and it's easy to get people to listen to you because of the desperate nature of the illnesses we're tying to treat.
- That would be my major take home lesson in terms of trying to deal with time and cost considerations. If you're wrong about the direction of things, change what you're doing and work with others because you can't have all the good ideas. You also should have an exercise where you predict how and where the technologies will fall short and fund that in parallel.

Q (Rich Voliet, UC Davis School of Veternary Medicine): Was production ever a problem? How do you get it into patients quickly and safely?

A: That's a subject I've thought a lot about. There was a point in time when you could do a clinical experiment and learn from the experience; mechanisms like investigator sponsored INDs were easy. Now because of mishaps along the way, there is a greater degree of oversight and regulation so I don't have an easy answer.

- Clinical research is under the microscope in a way it never has been before; there are more regulatory agencies involved rather than less and I don't know what the answer to that is. Perhaps education and letting the public know there is a price to pay for new therapeutic development. There are no perfect drugs, but the industry didn't do a good job of educating the public about that.

Q (Bob Klein): In clinical trials or applied research, there is a lot of information that's gained about the developmental biology of a disease from what does *not* work. That may have a positive feedback role in optimizing current clinical treatment but it would appear there's no way to capture that information. Is there positive value in creating a structure to capture more of what you learn about what doesn't work that may not be patentable but that has clinical feedback value in terms of enhancing current therapy?

A: Absolutely. What does not work is as much a teacher as what does. The value of increased scrutiny is there is much more information available on web, like through ClinicalTrials.gov.

- There is some discussion about to what extent clinical trials data will be made available prior to commercializing a product. That is controversial from a competition point of view, but just being able to track clinical trials allows you to go to that company and under confidentiality to get that information and learn from it.

- It's also important to gather information from ongoing clinical trials that may have nothing to do with stem cells but can teach us about disease and how to measure efficacy.

General Discussion
Moderator: Zach Hall, Ph.D., CIRM

Q (Zach Hall): What scientific strategies will be required to advance stem cell research from the laboratory to the clinic?

A (Ali Brivanlou, Rockefeller University): How do we set up what is really a priority? Maybe we should have a handle on the seventy cell lines that represent disease and attack the ones that are easiest to move forward.

- From Jill's talk, I learned about the importance of the "scientific readiness" of a project. To me, from a basic point of view, that would be a great place to start. We can use that as an approach to evaluate among all the things we can do, and decide which one to attack.
- Based on the assumption that we want something to work to establish the platform for everything else, maybe we need to focus on scientific readiness. What can we focus on that's closest to maturity? The best way to do this in the lab is to look at the data.
- At CIRM you can do this at a level that's much bigger. I would propose that we help define what is scientifically ready in the stem cell field.

Q (Zach Hall): Should we engage in that process ourselves?

A (Ali Brivanlou, Rockefeller University): Absolutely. Not without getting advice from the outside but among ourselves as scientists, as people working at the drug interface and doing clinical analysis of drug development. Can we get together and say this is where we are with disease X and prioritized based on that and move down the list?

A (Don Reed): I would like to see an outreach to the patient advocacy community to try to look at the symptoms that certain diseases may have in common. There are a lot of small diseases that may not be marketable but may have symptoms that fit in with those of other diseases. Maybe if this point was made clear that might be a way to find a way to work together to solve multiple things to find similarities among symptoms.

A (Alan Spiegel, Albert Einstein College of Medicine): I might invert that idea. I'm not sure that the commonality of symptoms will be informative from the therapeutic or preventative point of view. It might be helpful if what you're interested with is symptomatic relief. The germ of the idea is to find a set of rare diseases that seem different but where there could be commonalities in understanding the fundamental biology. There's a virtue of looking for areas of economies of scale and areas where you could make a contribution that cuts across a whole series of diseases. It may or may not pan out, but it would be an interesting heuristic principle.

A (Zach Hall): This is slightly reminiscent of the Canadian Stem Cell Network where they began by selecting diseases to focus on and after a couple of years they decided it wasn't working and tried to focus on enabling technologies. That doesn't mean you don't work on disease but you choose a problem based on technology and breadth and general interest.

A (Alan Spiegel): They're not mutually exclusive in the sense that you could have a generic approach that would cut across and involve enabling technologies but also do the mapping that was discussed and really see which specific diseases seem closest and most ripe. There is no low hanging fruit here, but some things may possibly be within reach. You could map things out, but how you get to those different steps is not clear, but if you could at least find that there is a scientific grounding for a few of these it would justify a more targeted approach while simultaneously a more broad-brush approach.

A (Stuart Orkin): Sometimes you don't appreciate these commonalities at the outset. For example, the target may be useful in one entity but be just as useful or more useful in another entity that may lag behind.

A (Zach Hall): It's the power of serendipity and the ability to be opportunistic as you explore one possibility and explore it application elsewhere.

A (Stuart Orkin): If we choose a disease we will almost certainly be wrong but it's good to think about those diseases that are closest to the front. But in a sense if you fail at that, and certainly pharma would say you will fail many times, was the investment good, and would you have been better off in investing earlier? I don't think we know the answer.

A (Zach Hall): As we evaluate grants this kind of thinking will have to play in. The idea of SMA may be useful in looking at the requirements to make this successful. That will have to be one of the criteria. Are the pieces in place to make this next step the right one and to move ahead or are there foundational pieces missing that you have to go back and pick up?

Q (Dennis Steindler; University of Florida, McKnight Brain Institute): If we want to advance the research from the lab into the clinic more quickly, maybe we could try to compare the animal models of disease with the animal stem cells we will try to use to fix those animal models to the human diseases that we really want to cure. What could help that process is to have more standardization of the animal models and animal stem cells we're using to cure those diseases. The same could hold for *in vitro* bioassays where we screen for biogenic factors that affect those cells. Mahendra Rao is an advocate of not comparing rodent to human stem cells.

- The behavior of cells in bioassays is very different from cells *in vivo* yet we try to draw conclusions from studies of animal cell and say if will be the same in humans. We need *in vitro* and *in vivo* screens well thought out and to have very robust bioassays for have high throughput screening of drugs that control fate decisions and differentiation. That will advance the field much more rapidly and we'll get things quicker form the lab to the clinic.

Q (Ken Taymor): As a member of the public, I want to ask: what do you as a collective community view as success?

- The initiative was presented to the public as research and cures. You've learned a lot and brought many people together within the strategic planning process and identified realistic criteria of success.
  - It struck me that there a great deal of private investment in Type 2 diabetes and less in Type 1. Would it be a success to have a cure for Type 2 diabetes a year or two before big pharma rather than letting the industry move forward with its investment instead of focusing on diseases where for various reasons there isn't currently private capital?

- Perhaps at its most extreme, the question is: is it a success or major failure if you find an approach that is successful in terms of affecting a cure but also renders obsolete private investment capital? Where is it appropriate to be competitive with private capital and where to be complementary?

A (Zach Hall): Let me make just make one point and it's important to stress this - we are not going to find a cure without private sector participation. We heard from Jill this morning that the NIH is prepared to pass this off and we heard from Steve about the long term investment required to develop therapies that we're not prepared to match.

- In our interviews, one of the questions we ask and one of the things we discussed before the last ICOC meeting is how we will define success. There are two things here: one is an aspirational goal and the other is the question of how will our success be measured by ourselves and others.
- Participation with industry is a strong component of success and we will have a meeting with representatives from industry on July 25th.

A (Stephen Sherwin): I wanted to make a comment on the issues around picking priority targets and add one consideration.

- In the area of funding for Type 1 vs. Type 2 diabetes, you're right - the industry has focused on Type 2. Form their standpoint, it's an expanding market.
- In areas of therapeutic product development based on new technologies, you can assume that for every believer there are 10 skeptics who believe there is a simpler, cheaper way to do the same thing than what you might accomplish with expensive technology. So the best targets in my mind are those than can *not* be readily accomplished with conventional approach to therapeutic product development.
- You can't find an area greeted with more skepticism bordering on antipathy in the scientific and medical community than gene therapy, but we will persevere in that area because we believe there is value in that technology and that it will be successful. I thought the most important thing we could do is put the technology on a target with a methodology that we know can't be achieved with another therapeutic product strategy. If you pick the targets where people will say there was no other way to get it done, the momentum with go from there.

A (Zach Hall): You have to have a competitive therapy.

A (Claire Pomeroy): It's interesting to see how our discussions have evolved but I'm struck by the fact that we tend to be linear thinkers and think if we gather the evidence we can pick the priorities. In this very young field, we will have to approach things differently and we need to set a timeline where we have a first inclusive set of approaches and have a formal consideration of which of these are accelerating. It's very premature to try to predict things otherwise.

- I also wonder if we went with this inclusive first phase if a diversified approach where we might put things into buckets and review them after 2 or 3 years would work. What about the techniques that we need - some of those are very young and maybe that's a bucket. Some disease specific approaches are a bucket. Can we use stem cells for screening drugs and is that a bucket? I'm not sure what all the right buckets are - certainly ethics and societal implications is one.
- Rather than decide which are the likeliest to pay off, we should admit we are too naïve and talk about the right buckets knowing we've set a deadline for each of these. We also need a mechanism in place to stop projects.

A (Zach Hall): The continuous evaluation of progress will be an important plan of our plan.

A (Don Reed): It would be great if we had a certain number of projects that are aiming for out of the ball park home runs. If we just get one home run, never again will this research be questioned.

A (Bob Klein): I'd like to echo Claire's earlier point that humility on our part might be well advised. There might be some great new brilliant ideas we maybe can't anticipate at this point. The Board has talked about providing seed money though innovation grants to prove out those initial concepts and get preliminary data so we can see what the opportunities are.

- While we are seeing these opportunities there may be some where the SMA advanced approach could be applied but we certainly have an obligation to ask for combined genius of the scientists in California through several broad innovation rounds where we seed what the possibilities before we start limiting down based on what's known.

A (Zach Hall): I think that's absolutely dead on. One of our interviews last week began with the interviewee saying that ten years is not a long period of time. In ten years we will still be gaining new information as well as bringing things we've started early in the project closer to fruition.

- We will continue to lay the groundwork for future discoveries. One issue is we don't know what those emerging technologies or those ideas are. There's a tendency to think we'll have a basic science phase and then a translational phase. We will have to develop all simultaneously though we may weight them differently at various points. Ten years is a short period of time to bring a therapy to fruition and even them it requiring tinkering and optimization. We will need to press forward on all those fronts.

Q (Zach Hall): Are there special projects or approaches where CIRM can make a unique contribution?

Q (Richard Volliet): One of the major areas is animal models. That's a tremendous resource that is not being utilized in the field. I submit that in mutant mice all you'll learn about is cells. If you want to advance the field almost every senior scientist says you need appropriate animal models. I think CIRM should invest time in making the research community aware of non traditional animal models.

- For example, we see about 100 dogs a year with untreated Type 1 diabetes. To me that's a resource that's amenable to therapy. There are some excellent animal models that will provide much more information. There's too much money spent on mice.

Q (Zach Hall): One member of the Strategic Planning Advisory Committee suggested that one of the unique things CIRM might do is put a large amount of money into a project to map gene expression in stem cell development. We heard from Allen that part of strategic plan at NIDDK was to have a comprehensive genomics approach and look at a series of pathways intensively. What are your thoughts about the interest and advisability of this approach? Is this a good thing to do or a bad thing to do? It might be hard for others to do.

A (Jeannie Fontana; Burnham Institute): I can't help but make the analogy with the investment community - we're diversifying our portfolio. Are we going to be Warren Buffet like and we pick a company or two we know well or will we like a hedge fund or like muni bonds..

- I think we should probably diversity and we should offer things other systems don't offer like the NIH isn't funding hESC research, so we should. It seems like we should provide a service that isn't already met.
- I do like Ali's comment about finding a disease or project we might get some success on, but I don't necessarily agree with the home run approach because you run the risk of failure. I think we should pick a project where we have a strong probability of success.
- We should also be mindful that the best defense is success because no one has been under the microscope like us. We need to be more sensitive to the public perception and the media's response to it and do it in a proactive way.

A (Stuart Orkin): I'd be very disappointed if CIRM invested in that genomics project. Scientists would love to have the information like it, but the greatest challenges are biological ones and that's what you could contribute. Maybe we should use technology to deal with the biological issues rather than a cataloging project.

Q (Jean Fontana): I have a question for Jill Heemskerk: Does the government just freely hand away licensing rights? What advice do you have for us as we're setting up our system?

A (Jill Heemskerk): We'll handle the IP on a case by case basis. What we've done in the first case where the NIH has filed a provisional patent application is while we clearly have to license that opportunity to industry, the way NIH handles licensing opportunities is to get as many licenses as possible out of any given invention. While historically the NIH has given away licensing rights without royalty encumbrances, there as been backlash so there is a trend to try and predict the value of licenses and try to recover some of that for the NIH so that more can go into this kind of research.

- One thing I keep hearing come up is the fear of failure, that if you pick something and go for it you run the risk of failure. We recognized that in developing the SMA project, but what shouldn't be undervalued is the benefit of failing in a careful, thoughtful way. You don't predict failure, so when you do fail, you learn something you didn't know. Philosophically, I would caution against fear of failure.

Joan Samuelson, J.D., Parkinson's Action Network
Vice Chair, CIRM Scientific and Medical Research Funding Working Group

- It seems to me that as we grope toward how we'll spend the money strategically, one thing we can do is identify a set of principles. Some that seem obvious to me are we need this to be done boldly and with a sense of urgency. Proposition 71 commands we get this done as fast as possible.

- We need boldness and urgency at every turn and going with that is the desirability of having patients and their loved ones sprinkled throughout the decision making process, not to supplant the scietific expertise of those who will be engaged, but to offer a sense of urgency and an innate sense of priority setting that really can benefit our decision making.

- I also want to echo what Jill said about risk taking. It seems to me from what little I've read about the history of the development of effective therapies is that failure is an inevitable part of success.
  - The people of California are ready for something wildly ambitious because many of those who have a disease innately get the fact that this will have to be done in a way that risks failure. And we can explain that risk and people will understand and get it and they will be happy we're taking that approach especially when we remind them of the daily toll of the status quo. So if someone is hurt in a clinical trial that's a drop in the bucket of the misery that goes on every day because of disease.

- Another principle I would suggest is that we engage in the development of our strategic plan and priority setting, which will have to be seen to be successful and use money effectively and efficiently, is to do that as best we can in a virtual, global way.
  - We should use information to the extent it exists and to the extent it doesn't we should try to get a system set up so we're benefiting from the wisdom and successes and failures of those elsewhere engaged in similar or related tasks.

- I also want to ask if the NIH's Human Genome Research Institute, or anyone else who has money for that kind of research but not for the therapeutic end result, could partner with us in any respect in any of this.
  - Maybe there's a set of questions we have to ask to see if the idea makes the cut and if anyone else do it so our money is only used for the highest and best purposes, that is, getting things done as quickly as possible.
  - We should communicate to the people of California that that's what we're doing because that will soften the blow when there's a failure or things don't go as fast as they would like because they will see how hard we're working to be efficient with the money and to move with a sense of urgency.

Q (Zach Hall): Your point is dead on that science comes with failure but we're not sure how readily the public will respond to that.

A: One thing I've noticed in the work in the Parkinson's field is a sense of aversion to failure that when a very public clinical trial didn't reach the desired results it was almost like it was a scandal and it dropped from sight and the many questions that could be explored weren't. So maybe there's a set of principles that could be added that pertain to that.

General Discussion, cont'd
Moderator: Zach Hall, Ph.D., CIRM

A (Steve Sherwin): We have to worry about high profile kinds of failure, like the Jesse Gelsinger case, which is to be avoided at all costs. Those things should not be tolerated and should be avoided. But there's failure and there's failure. The second thing is, if the end result of

a clinical trial is negative but it's been done rigorously and carefully and we've leaned something fundamental that will inform future efforts, that's not a failure.

- The problem with some studies is there is a tendency that if a thing works it's magnificent but you may not have a clue why, it may not be replicable, and if it doesn't work you haven't learned a thing. That's more relevant. We should be bold but in a way that lets us learn from things that don't work.

A (Ali Brivanlou): Maybe I can bridge between these descriptive and genomics approaches with an appreciation of urgency; maybe these should go side by side. As embryologists, we learn that cell fate is set by a hierarchy of decision making that happens in time and space. It's amazing to me that we know more about this aspect of the frog and mouse embryo than our own. Human embryology is nonexistent and not fundable by the NIH. Let's be the Christopher Columbus of the embryo and map all the genes expressed in stem cells and maybe in the first week or two of gastrulation and learn form the way the embryo does things. If you know where the players are at a given time and space you can address the function better than if you didn't know.

- Maybe CIRM can have a historic impact here by providing what we need to base all our funding and discoveries on. Of course, there are issues of where we will get these embryos. But we have the genome in our pocket, and the name of the game is to map all the genes we know about and try to correlate events at the differentiation level to the process of fate determination so we can understand how an embryo does it.

A (Dennis Steindler): I'm a stem cell researcher who has people in my lab working on stem cells in an environment that's not extremely conducive. With what you have here in California, it makes sense you have an environment to study ESCs that is unique and that is user friendly for all the excellent science that already goes on in California. So if you superimpose that environment to the type of developmental biology Ali is talking about and the great institutions in this state that will answer both those questions.

A (Bruce Conklin): I want to comment on the proposal for the expression project. Doing gene expression analysis is a bad idea for CIRM to fund because the NIH is funding this already. Also, there are lots of gene expression studies with H9 cells.

- The problem, which I have in my own lab, is with the baseline data on the stem cells that are non-presidential. There is so much baseline data on H1 or H9 cells that we know what is expressed with these cells, but we don't know what's in Melton's stem cells or some from Sweden's, so there's a vicious cycle where because we don't have the baseline data from these genetically diverse and interesting lines that do not have presidential approval it's hard to make a rationale for doing some experiments.
- To get that baseline data would cost a lot of money. If we had information not only about gene expression but also gene sequence, those sorts of baseline data, people should be reaching towards non-presidential cell lines because there is information there and they should be screaming for it in Missouri and Ohio. Once we get that baseline information, it will be hard to get people <u>not</u> to work on those cell lines. We have to break the chicken or the egg cycle and that's part of it.

Q (Zach Hall): What is CIRM's role in supporting clinical research and / or the clinical development of therapies?

Q (Zach Hall): One of the speakers at our meeting in October made an eloquent plea that because university clinicians have to depend on industry for the money to do even early stage clinical trials, they are constrained by the questions they can ask and the information they can get. This same person said we need to learn from failures, so it is probably important to set up to do more academic type trials and having the wherewithal to do that.

- We also spoke with someone in our interviews in the area of clinical development in industry who said "Don't waste your time. The only people who have the money to do this are in the private sector. I have a big machine at my disposal that I can point at any problem, but it's incredibly expensive, and it's expensive in ways you wouldn't believe." So the question is, would it be helpful for CIRM to provide an infrastructure for such trials in academic settings? Is that a worthwhile thing to do?

A (Alan Spiegel): The more tests you do you the more you are limited by recruitment issues. To the extent you have the money to do it, it is a nice add-on. There may be no downside to having these additional studies done and it may be a value added.

- We met with heads of research at pharma and others and most of them said don't even bother; this may be true for medicinal chemistry and small molecules, but are there examples where industry has a heavy investment in cell therapy? To the extent that *ex vivo* culture, scale up, and delivery of cells has been done, I am not sure. To the extent there is a gap, it may be expensive and difficult but there may be a unique role.

A (Ed Penhoet, Vice-Chair, ICOC): We should not confine our support of clinical trials to academic settings. There is precedent of foundations, which are goal oriented, funding trials in companies and the clinical trial may be where we get the most benefit in filling in the gap. So we shouldn't limit ourselves to thinking about trials in the academic setting.

- As a related point, collaboration has been mentioned many times and we have to ask what CIRM's role will be. Strategically, will we take a goal oriented and proactive approach to facilitate and drive collaboration or a responsive funder of collaboration?

A (Stephen Sherwin): There are three ways CIRM can be involved in supporting clinical research:

- By supporting academic, small-scale clinical trials that will address questions not addressed by industry sponsored trials. To make that happen, one area of funding support to consider is to provide the regulatory structure to assist getting through approval which will only be greater for stem cell therapies.
  - Consider a network of academic centers funded through a contract similar to an NIH model. The funding would be to set for what's necessary to do clinical trials in today's world of extraordinary regulation, so you would provide support for relatively mundane things, such as study coordinators and study monitors. It's mundane and not science but would be hugely beneficial to assist us to move through this. Those centers in your network could be mobilized to do specific, small Phase I/II trails.
  - It troubles me the disappearance of that kind of clinical trial because academic centers cannot navigate the regulatory minefield and this is a business.
- There is no question that companies can't do anything without support of the patient groups. Patient advocacy groups will be essential for successful, large-scale clinical trials.

I know from experience in the 1980s that the HIV community was instrumental in the conduct of clinical trials. I think this organization could consider how to be a channel for advocacy groups for disease targets. It's a currency you have that industry will want and at the end of the day it is quid pro quo.

- Role in advocating policy that can really make a tremendous difference. I don't know whether that's pertinent. One investment that will pay back in terms of shortening trial timelines is to provide additional baseline funding to the FDA. If that agency is not supported to generate new regulatory policy, you will have huge slow-downs later.

A (Burt Lubin, Children's Hospital of Oakland): We also have an obligation to address the minority communities in this state and help disparities. Issues related to SCNT experiments may focus on where the donors come from and which people will be willing to donate. There will be major sociologic and legal issues for us to consider as we move forward.

Final Comments

Q (Zach Hall): Are there any final comments?

A (Joan Samuleson): I do see us as having the role of a principle facilitator and developer on a global level. I think leading in showing the role of patients integrated into this strategic effort is a piece of that and is extremely important.

- Let me give you an example: It was before the NIH RAC and the issue was whether they would permit a clinical trial to go ahead in Parkinson's. They had two applications, one for Alzheimers, and one for Parkinson's, and the issue of urgency was an underlying factor.
- I decide my role should be exampling how my morning had gone and the many struggles I had preparing for that meeting. Talking about my morning turned that analysis around and they approved it on the spot. This is an era of the emergence of patient advocacy so we might as well be proactive in showing how that can be used as an integrated piece of this sort of strategic scientific effort.